# The Flavor and Fragrance High Production Volume Consortia

## The Terpene Consortium

## Test Plan for Terpenoid Primary Alcohols and Related Esters

| | |
|---|---|
| **3,7-Dimethyl-6-octen-1-ol (dl-Citronellol)** | **CAS No. 106-22-9** |
| ***trans*-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol)** | **CAS No. 106-24-1** |
| ***cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol)** | **CAS No. 106-25-2** |
| **Acetylated myrcene (Process name for mixture containing *cis*-and *trans*-3,7-dimethyl-2,6-octadien-1-yl acetate)** | **CAS No. 68412-04-4** |

**FFHPVC Terpene Consortium Registration Number 1101125**

**Submitted to the EPA under the HPV Challenge Program by:**

**The Flavor and Fragrance High Production Volume Chemical Consortia**

**1620 I Street, NW, Suite 925**

**Washington, D.C. 20006**

**Phone: 202-331-2325**

**Fax: 202-463-8998**

# List of Member Companies

**Arizona Chemical**

**BASF**

**Bush Boake Allen, Incorporated**

**Citrus and Allies Essences, LTD**

**Givaudan Roure**

**ICI Americas**

**International Flavors and Fragrances Inc.**

**J. Manheimer Incorporated**

**Hercules Chemical**

**Millennium Chemicals, Inc.**

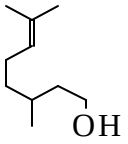
**TECNAL Corporation**

**Universal Flavor Corporation**

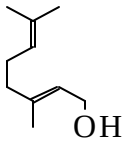
# Table of Contents

# The HPV Challenge Test Plan for Terpenoid Primary Alcohols and Related Esters

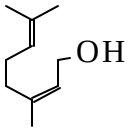
## 1 Identity of Substances



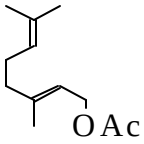

**3,7-Dimethyl-6-octen-1-ol**
**(dl-Citronellol)**
**CAS No. 106-22-9**




***trans*-3,7-Dimethyl-2,6-octadien-1-ol**
**(Geraniol)**
**CAS No. 106-24-1**




***cis*-3,7-Dimethyl-2,6-octadien-1-ol**
**(Nerol)**
**CAS No. 106-25-2**




***trans*-3,7-Dimethyl-2,6-octadien-1-yl acetate**
**(Acetylated myrcene - principal component)**
**CAS No. 68412-04-4**

# 2 Category Analysis

## 2.1 Introduction

In October of 1999, members of the U.S. flavor and fragrance industries and other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia are committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The Terpene Consortium, as a member of FFHPVC serves as an industry consortium to coordinate testing activities for terpenoid substances under the Chemical Right-to-Know Program. Twelve (12) companies are current members of The Terpene Consortium. The Terpene Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and, where needed, conducting additional testing. The test plan, category analysis and robust summaries presented below represent the first phase of the Consortium's commitment to the Chemical Right-to-Know Program.

## 2.2 Background Information

The chemical category designated "Terpenoid Primary Alcohols and Related Esters" includes three terpenoid acyclic aliphatic primary alcohols, citronellol, geraniol, and nerol. The category also includes a mixture of terpenoid esters and alcohols called acetylated myrcene. Geranyl acetate and neryl acetate are the principal products formed when myrcene is acetylated. Thus, the mixture is commonly recognized as acetylated myrcene. The four substances are grouped together because of their close structural relationships and the resulting similarities of their physio-chemical and toxicological properties. In nature, terpenes are produced by the isoprene pathway that is an integral part of normal plant and animal biosynthesis. Oxygenated terpene substances {e.g., geraniol, nerol, citronellol, citral (a mixture of geranial and neral), and geranyl acetate} are therefore, ubiquitous in the plant kingdom. They are also common components of

traditional foods. Quantitative natural occurrence data indicate that oral intake of these substances occurs predominantly from consumption of food in which they occur naturally [Stofberg and Grundschober, 1987; Stofberg and Kirschman, 1985]. Greater than 500,000 pounds (lbs) of citral, citronellol, geraniol, nerol, and related esters are consumed annually as natural components of food in the United States. Less than 25,000 lbs of the four substances in this chemical category are consumed annually as added flavoring substances in the United States [Stofberg and Grundschober, 1987]. Citronellol, geraniol, nerol, and geranyl acetate are currently recognized by the U.S. Food and Drug Administration (FDA) as GRAS ("generally regarded as safe") for their intended use as flavoring substances [Hall and Oser, 1965].

In addition, geraniol is endogenous in animals. As the pyrophosphate and coenzyme A (CoA) esters, geraniol is present in all cells as an intermediate in cholesterol biosynthesis. Although all cells have the potential to produce cholesterol, greater than 90% of production occurs in the liver and gut. In the biosynthesis of cholesterol, isopentyl pyrophosphate and an isomer, dimethylallyl pyrophosphate, both 5 carbon fragments, are condensed to yield geraniol CoA, a $C_{10}$ fragment. Isopentyl pyrophosphate transferase then mediates the addition of a second isopentyl pyrophosphate moiety to geraniol CoA yielding farnesyl CoA, a $C_{15}$ fragment. Two farnesyl molecules condense to yield squalene, a $C_{30}$ fragment that is eventually cyclized to yield cholesterol [Voet and Voet, 1990; Stein, 1986].

## 2.3 Structural Classification

Citronellol, geraniol, and nerol are close structural relatives. Nerol and geraniol are *cis/trans* isomers of 3,7-dimethyl-2,6-octadien-1-ol and citronellol is the dihydro analogue of geraniol (3,7-dimethyl-6-octen-1-ol). Acetylated myrcene is a process name for the product obtained from the acetylation of the terpene hydrocarbon, myrcene. The product is predominantly (60-65%) a mixture of the acetate esters of nerol (*cis*-3,7-dimethyl-2,6-octadien-1-ol) and geraniol (*trans*-3,7-dimethyl-2,6-octadien-1-ol). The *trans* isomer, geranyl acetate (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate) is the

principal component of the mixture. Minor components include the non-esterified alcohols nerol and geraniol (2.5%) and another terpenoid ester, linalyl acetate (2.5% - also reviewed under "FFHPVC terpenoid tertiary alcohols and esters" to which reference should be made for all relevant data). The only other major component is limonene (10% - a widely naturally occurring terpene that is reviewed under "FFHPVC terpenoid aliphatic hydrocarbons – limonene group" to which reference should be made for all relevant data). No other component of this mixture exceeds 3%.

Based on their structural similarities, these substances are expected to have virtually identical physical, chemical and biological properties (see Test Plan, section 3). The available data support this conclusion. Acetylated myrcene (geranyl and neryl acetate), being the mainly a mixture of esters, is expected to be somewhat less polar and therefore less water soluble that the three terpenoid alcohols. It is however, expected to be rapidly hydrolyzed *in vivo* to yield nerol, geraniol, and acetic acid [Grundschober, 1977]. Similar hydrolysis also occurs in the environment albeit at a somewhat slower rate [AOPWIN].

Citronellol, geraniol and nerol and the principal hydrolysis products of acetylated myrcene (geranyl acetate) were all included as structural similar acyclic terpenes in a QSAR study by molecular orbital calculations for prediction of their potential toxicity/carcinogenicity [Lewis *et al*., 1994]. None of the substances in this group were predicted to have significant toxicity and/or carcinogenicity potential. This conclusion is supported by the results of a 2 year bioassay on a mixture of acetate esters of geraniol and citronellol that showed no toxic or carcinogenic effects at dose levels up to 2000 mg/kg bw/day in rats and 1000 mg/kg bw/day in mice [NTP, 1987].

## 2.4 Industrial and Biogenic Production

Since geraniol is used to prepare citral (a mixture of geranial and neral), an important flavor and fragrance material and an intermediate in Vitamin A synthesis, large-scale synthesis of geraniol has been developed. Production via synthesis now far exceeds isolation from essential natural oils such as citronella oil [Bauer and Garbe, 1985]. Nearly

all commercially available, technical grade geraniol is produced from pinene. In this process pinene is pyrolyzed to myrcene, which is converted into geranyl and neryl chloride. The chloride mixture is then converted to a geranyl/neryl acetate mixture, which is subsequently hydrolyzed and fractional distilled to yield geraniol (98% pure) and nerol [Weiss, 1959]. In recent years, commercially available geraniol has become available as a product of linalool isomerization. Isomerization using *ortho*-vanadate catalysts yields a 90% mixture of geraniol and nerol, which may be further purified via distillation [Yoshiaki *et al.*, 1973].

As common plant monoterpenoids, geraniol, nerol, and citronellol and their esters are ubiquitous in the environment. Accurate estimates of the environmental production of these substances is complicated by the fact that most if not all vegetation produces these alcohols and esters. However, estimates of biogenic production are critical to the determination of the sources of emission into the environment. Arguably, if background biogenic production and subsequent emission of terpenoid alcohols exceed industrial (anthropogenic) production and emission by orders of magnitude, no significant environmental impact can be expected.

Environmental monitoring has detected ambient atmospheric [Larsen *et al.*, 1997] and aquatic [Heil and Lindsay, 1990] levels of terpenoid alcohols. Trace levels of geraniol, nerol, and geranyl acetate were first detected in coniferous and deciduous plants in the early $20^{th}$ century (*e.g.*, eastern hemlock, spruce and Douglas fir [Guenther, 1952]). The fresh twigs and adherent leaves of Douglas fir from Washington State, Colorado, England, and Italy all show measurable levels of geraniol, nerol and geranyl acetate [Guenther, 1952].

To gain a perspective on the magnitude of annual biogenic production of terpenes including terpenoid alcohols, consider the production of geraniol by a common evergreen predominant in the Western United States. Geraniol concentration in new growth fir twigs and needles in Washington State Douglas fir has been estimated to be 0.9 kg/1000kg [Johnson and Cain, 1937]. Since new growth of twigs and needles is a

dynamic process occurring annually, the value of 0.9 kg/1000kg approximates annual production of geraniol by Douglas fir. Based on a Douglas fir canopy of 80 trees/acre, a conservative annual mass yield of 80 kg new growth/tree, and 31,000,000 acres of Douglas fir in the West, it is estimated that annual biogenic production of geraniol approaches 200,000,000 kg [Curtis, 1982, 1994]. This estimate is extremely conservative since it considers biogenic production only by Douglas fir from a single region, the Western United States: it disregards all other plant production of geraniol and biogenic production from other regions of the United States.

Based on the above conservative estimates, annual biogenic production (200,000,000 kg) of geraniol is at the very least 20 times annual industrial production (9,000,000 kg) [TSCA, 1990]. Similar estimates can be made for other members of the chemical category (see Table 1).

***Table 1. Annual Industrial and Isolated Biogenic Production of Terpenoid Alcohols***

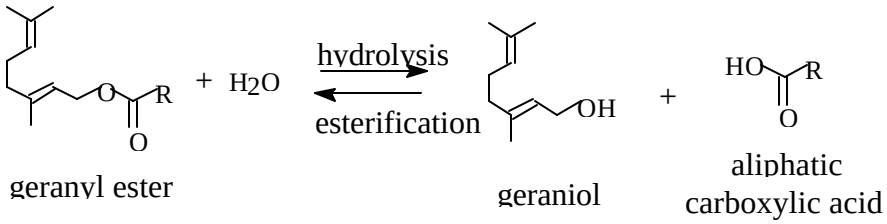
| **Substance** | **Annual Industrial Production, kg (TSCA, 1990)** | **Annual Biogenic Production by U.S. Douglas Fir, kg** |
|---|---|---|
| Geraniol | 9,000,000 | 200,000,000 |
| Nerol | 3,200,000 | 12,000,000 |
| Citronellol | 1,800,000 | 10,000,000 |
| Acetylated Myrcene | 1,000,000 | 8,000,000 |

## 2.5 Chemical Reactivity and Metabolism

### 2.5.1 Hydrolysis of Geranyl Acetate and Neryl Acetate

The ester, geranyl acetate, is expected to hydrolyze to geraniol and acetic acid (see Figure 1). In animals including fish, hydrolysis of aliphatic esters is catalyzed by classes of enzymes recognized as carboxylesterases or esterase [Heymann, 1980], the most important of which are the *B*-esterases predominating in the hepatocytes [Anders, 1989; Heymann, 1980]. A concentration of 15 ul citronellyl acetate/L was reported to be completely hydrolyzed within 2 hours by simulated intestinal fluid containing pancreatin at pH 7.5. A concentration less than 18 ul citronellyl phenylacetate/L was reported to be 60% hydrolyzed within 2 hours at pH 7.5 [Grundschober, 1977]. Terpenoid alcohols formed in the gastrointestinal tract are then rapidly absorbed [Phillips *et al.*, 1976; Diliberto *et al.*, 1988].

***Figure 1. Hydrolysis of Geranyl Esters***



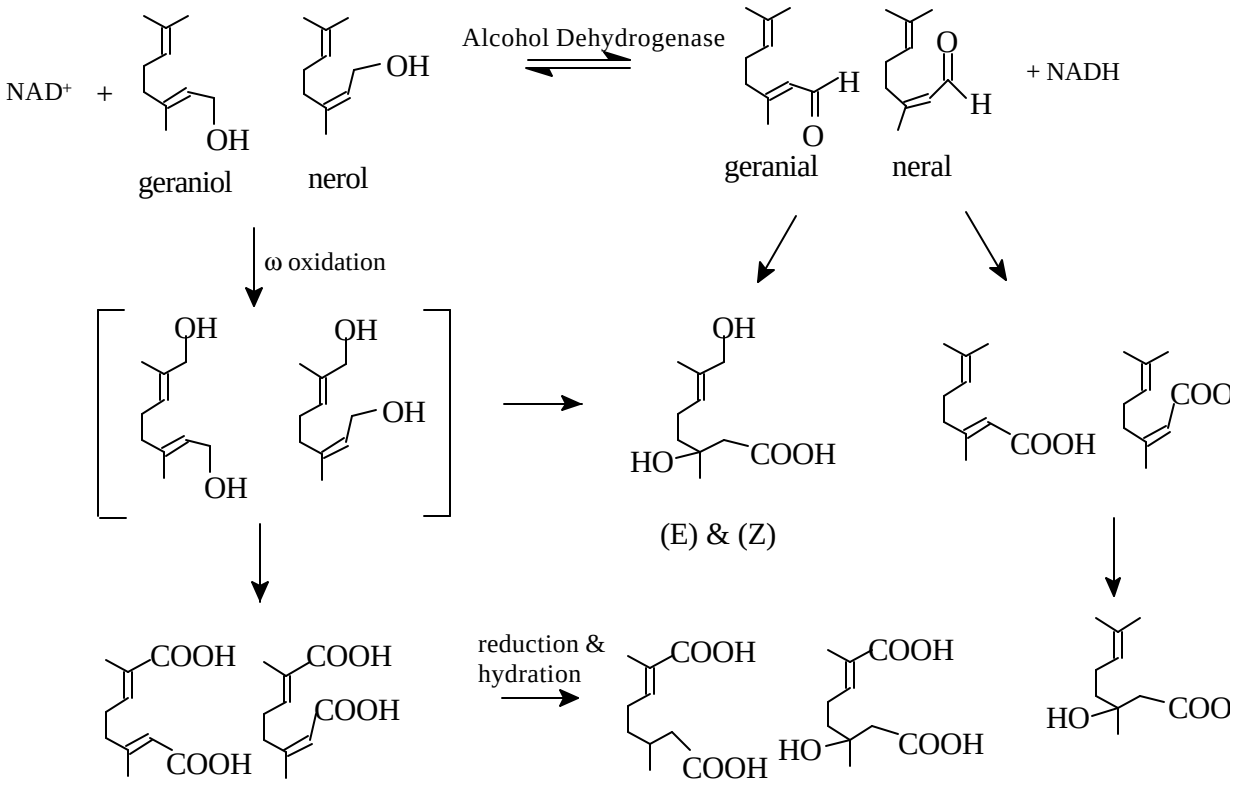

Carboxylesterase (Type B) activity has been reported in a variety of fish species at different life stages [Leinweber, 1987; Boone and Chambers, 1996; Abas and Hayton, 1997; Barron *et al.*, 1999]. Enzyme activity of rainbow trout sera, liver and whole body homogenates were similar to those of rat liver homogenate. A significant increase (300%) in activity occurred between yolk-sac and juvenile stage of rainbow trout development. Carboxylesterase activity was not significantly different for whole body homogenates of the rainbow trout, channel catfish, fathead minnows, and bluegill [Barron *et al.*, 1999].

These data support the conclusion that simple terpenoid esters including geranyl acetate are readily hydrolyzed in these animals.

### 2.5.2 Metabolism

Following hydrolysis, geraniol, nerol, and citronellol undergo a complex pattern of alcohol oxidation, *omega*-oxidation, hydration, selective hydrogenation and subsequent conjugation to form oxygenated polar metabolites, which are rapidly excreted primarily in the urine of animals. Alternately, the corresponding carboxylic acids formed by oxidation of the alcohol function may enter the *beta*-oxidation pathway and eventually undergo cleavage to yield shorter chain carboxylic acids that are completely metabolized to carbon dioxide [Williams, 1959]. Geraniol, related terpenoid alcohols (citronellol and nerol), and the related aldehydes (geranial and neral) exhibit similar pathways of metabolic detoxication in animals (see Figure 2).

***Figure 2. Metabolism of Geraniol and Nerol in Rats***



Male rats were given repeated oral doses of 800 mg [1-$^{3}$H]-geraniol/kg bw by gavage daily for 20 days. Five urinary metabolites were identified *via* two primary pathways. In one pathway, the alcohol is oxidized to yield geranic acid (3,7-dimethyl-2,6-octadienedioic acid) which is subsequently hydrated to yield 3,7-dimethyl-3-hydroxy-6-octenoic acid. In a second pathway, the alcohol undergoes *omega*-oxidation mediated by liver cytochrome P-450 [Chadha and Madyastha, 1982] to yield 8-hydroxygeraniol. Selective oxidation at C-8 yields 8-carboxygeraniol which undergoes further oxidation to the principal urinary metabolite 2,6-dimethyl-2,6-octadienedioic acid ("Hildebrandt's acid") [Chadha and Madyastha, 1984] (see Figure 2). In rat microsomes, the C-8 methyl group of geraniol or nerol utilizes $NADP^{+}$ and $O_2$ and undergoes stereoselective *omega*-hydroxylation to yield the (E)-isomer of the corresponding diol [Licht and Corsia, 1978]. In rats, the corresponding aldehyde, geranial and its (Z)-isomer, neral, are metabolized *via* similar alcohol and *omega*-oxidation pathways [Diliberto *et al.*, 1990].

Geraniol and citronellol exhibit a similar metabolic fate in rabbits. Geraniol orally administered to rabbits by gavage is metabolized to 2,6-dimethyl-2,6-octadienedioic acid ("Hildebrandt's acid") and 2,6-dimethyl-2-octendioic acid ("reduced Hildebrandt's acid"), which are excreted in the urine [Fischer and Bielig, 1940]. In rabbits, d-citronellol is also metabolized to 2,6-dimethyl-2-octendioic acid ("reduced Hildebrandt's acid") [Asano and Yamakawa, 1950]. An alcohol precursor to "reduced Hildebrandt's acid" (8-hydroxy-3,6-dimethyl-6-octenoic acid) has been reported as a urinary metabolite in rabbits given citronellol by gavage [Fischer and Bielig, 1940]. The corresponding aldehyde citronellal undergoes *omega*-oxidation mediated by liver cytochrome P-450 [Chadha and Madyastha, 1982] to yield "reduced Hildebrandt's acid" [Ishida *et al.*, 1989].

In rats and mice, a mixture of geranial and neral commonly recognized as citral undergoes rapid absorption from the gastrointestinal tract and distribution throughout the body [Phillips *et al.*, 1976]. Approximately 60% of an oral dose of $^{14}C_1$ or $^{14}C_2$-labelled

citral was eliminated in the urine with approximately equal amounts of remaining radioactivity appearing in the exhaled air and feces within 24 hours [Diliberto *et al.*, 1988]. The $CO_2$ arose from rapid oxidation of the aldehyde and decarboxylation of the resulting acid. Although excretion in the feces was not a primary route of elimination, a significant quantity of citral was present in the bile [Diliberto *et al.*, 1988] suggesting that citral readily enters enterohepatic circulation. This is consistent with the observations that citral induces hepatic cytochrome P-450, glucuronyl transferase and alcohol dehydrogenase [Parke and Rahman, 1969; Boyer and Petersen, 1990].

In rats, citral is metabolized to a mixture of diacids and hydroxy acids resulting from *omega*-oxidation, reduction and hydration of the unsaturation at C-2, and oxidation of the aldehyde function [Diliberto *et al.*, 1990] (Figure 1). Greater than 50% of an oral dose of citral was excreted in the urine as diacids and hydroxy acids within 24 hours. Although the only metabolites observed in the urine are those derived from oxidation of the aldehyde function, hepatic reduction of the aldehyde may precede oxidation pathways. Citral is rapidly reduced to the corresponding alcohol-by-alcohol dehydrogenase (ALD) in rat hepatic cytosolic fractions [Boyer and Petersen, 1990].

Citral is not oxidized by mitochondrial aldehyde dehydrogenase and is a potent inhibitor of ALD-mediated oxidation of acetaldehyde [Boyer and Petersen, 1990]. Since geranial and the corresponding alcohol geraniol form analogous urinary metabolites [Chadha and Madyastha, 1984], it is reasonable to assume that geranial is reduced to geraniol, which is a substrate for cytochrome P-450 mediated *omega*-oxidation.

## 2.6 Summary for Category Analysis

In summary, geranyl acetate is rapidly hydrolysed in animals. The alcohols geraniol, nerol, and citronellol are efficiently detoxicated by two principal pathways in animals. In one route, the alcohols are successively oxidized to the corresponding aldehydes and carboxylic acids, the latter of which are selectively hydrated or reduced. In a second route, the aldehydes undergo reduction to the corresponding alcohols that are substrates

for *omega*-oxidation to eventually yield diacids and their reduced or hydrated analogs. Polar metabolites formed *via* these two pathways will be efficiently excreted primarily in the urine as the glucuronic acid conjugates. The physiochemical and toxicological properties of these three alcohols are consistent with their known reactivity and common metabolic fate.

# 3 Test Plan

## 3.1 Chemical and Physical Properties

### 3.1.1 Melting Point

These are relatively low molecular weight liquids with expected melting points well below 0°C.

### 3.1.2 Boiling Point

While none of the reported boiling points were obtained according to OECD guidelines, the consistency of the values reported by the Fragrance Materials Association [FMA] for citronellol, geraniol and nerol (range 225 °C to 230 °C) and in standard reference sources [Merck Index, 1997] confirms their reliability. The narrow range for boiling points is consistent with the fact that the three substances are $C_{10}$ alcohols that differ in molecular weight by 2 daltons (154 to 156 daltons) and are either *cis/trans* isomers or dihydro derivatives of one another. No boiling point is available for acetylated myrcene, however the principle components have boiling points as follows: neryl acetate – 231 °C; geranyl acetate – 244 °C [FMA]. The mixture, acetylated myrcene, would therefore be expected to boil in the same range as citronellol, geraniol and nerol.

### 3.1.3 Vapor Pressure

While the reported vapor pressure for citronellol, 0.0095 kPa at 30°C [Vuilleumeir *et al.*, 1995], was not obtained according to OECD guidelines, the agreement with the calculated values reported by the FMA at 20 °C (0.009 kPa for citronellol, 0.003 kPa for geraniol, and 0.008 kPa for nerol) confirm the reliability of all values. A vapor pressure of 0.009 kPa [FMA] for a mixture of the corresponding aldehydes geranial and neral is slightly greater than that for the corresponding alcohols nerol and geraniol. This is expected given the increased polarity and decreased volatility of the alcohol relative to the aldehyde. No vapor pressure is available for acetylated myrcene. However the

principle components have vapor pressures as follows: neryl acetate – 0.003 kPa; geranyl acetate – 0.004 kPa; limonene – 0.16 kPa. The components of acetylated myrcene would therefore be expected to have a vapor pressure in the same range as citronellol, geraniol and nerol.

### 3.1.4 Octanol/Water Partition Coefficients

The calculated log Kow values as reported by Syracuse Research Corporation [SRC], for citronellol, geraniol and nerol are very consistent and are in the range from 3.45 to 3.47. The reliability and conservative nature of these figures are confirmed by the measured log Kow of 3.1 for citronellol [Givaudan-Roure, 1991]. No octanol/water partition coefficient is available for acetylated myrcene, however, the principle components have calculated log Kow values [SRC] as follows: neryl acetate – 4.48 kPa and geranyl acetate – 4.48 kPa. Limonene has a measured log Kow of 4.57. The mixture, acetylated myrcene, would therefore be expected to have a log Kow of about 4.5. Decreased solubility of geranyl acetate compared to that for geraniol is expected given that geranyl acetate is an ester and lacks a polar alcohol functional group that increases water solubility.

### 3.1.5 Water Solubility

While the reported water solubilities were not obtained according to OECD guidelines, the agreement of the values reported, 600 mg/L for citronellol and 300 mg/L for geraniol, [BBA, 1990] with the calculated values [ESPOW], 211, 256 and 256 mg/L for citronellol, geraniol and nerol, respectively, support their reliability. No water solubility data are available for acetylated myrcene. However, the principle components being esters have lower solubilities than their component alcohols. The calculated water solubilities of neryl acetate and geranyl acetate are both 6.9 mg/L. The other major component, limonene has a calculated solubility of 3.1 mg/L.

### 3.1.6 New testing required

None

## 3.2 Environmental Fate and Pathways

### 3.2.1 Photodegradation

The calculated photodegradation half lives [AOPWIN] for citronellol, geraniol and nerol are in the range from 19 minutes to 1.3 hours. Acetylated myrcene can be expected to be in the same range since the calculated half-life for it's principal constituents, neryl acetate and geranyl acetate, is 19 minutes and for the second major constituent, limonene, is 37 minutes. Structurally, these substances are unsaturated primary alcohols that have the potential to form radical species in the gas phase and also be oxidized to the corresponding unsaturated aldehyde. The known chemical reactivity of these substrates supports short photodegradation half-lives predicted by the model.

### 3.2.2 Stability in Water

No hydrolysis is possible for the three terpenoid primary alcohols, citronellol, geraniol and nerol. All three are expected to be very stable in aqueous solution. The principal constituents of acetylated myrcene, geranyl acetate and neryl acetate are esters and are calculated to have half-lives for hydrolysis of 23 days at pH 8 and 231 days at pH 7 [AOPWIN]. Complete (100%) hydrolysis for citronellyl acetate was measured in simulated intestinal fluid at pH=7.5 [Grundschober, 1977]. Therefore, hydrolysis of geranyl acetate and neryl acetate is expected both *in* vivo and in the environment. The second major constituent of acetylated myrcene, limonene, will not hydrolyse in water. The significance of calculated half-life data for geranyl acetate must take into account the experimental data that aliphatic ester, in general, are readily hydrolyzed in fish [Barron *et al.*, 1999].

### 3.2.3 Biodegradation

Duplicate studies on citronellol and geraniol show these materials to be readily biodegradable (*i.e.,* 100% biodegradation by OECD 301B, OECD 301C, or DOC - Method F from Blue book series, 1991) [BBA, 1990; Givaudan-Roure, 1989; Quest, 1994]. Likewise, a mixture of geranial and neral (citral) exhibits greater than 92%

(OECD 301B) [Quest, 1994] and 99.5% biodegradation (DOC - Method F from Blue book series, 1991) [BBA, 1990]. Nerol is a stereoisomer of geraniol and would likewise be expected to be readily biodegradable. Geranyl acetate has also been shown to be readily biodegradable (greater than 82% biodegradation) [Birch and Fletcher, 1991] and, therefore, neryl acetate would be as well. The other significant constituent of acetylated myrcene, limonene, has not been shown to be readily biodegradable. However, since limonene makes up only 10% of the mixture, a ready biodegradation test of the mixture is expected to result in apparent ready biodegradation. In summary, all members of the chemical category are expected to readily biodegrade in the environment.

### 3.2.4 Fugacity

Transport and distribution in the environmental were modeled using Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11 [Mackay, 1991]. The principal input parameters into the model are molecular weight, melting point, vapor pressure, water solubility, and log Kow. Where measured values were available, these were used but where they were not, calculated data from the EPIWIN series of programs were used. Based on the comparable physiochemical properties of the three alcohols (geraniol, nerol, and citronellol), it is not unexpected that the three would exhibit similar distribution in the environment. Since acetylated myrcene (geranyl acetate) is hydrolyzed, it forms geraniol in the environment. The significance of these calculations must be evaluated in the context that the substances in this chemical category are products of plant biosynthesis and are, therefore, ubiquitous in the environment. Most have been shown to be readily and/or ultimately biodegradable, and the remainder would be expected to behave similarly in the environment. The model does not account for the influence of biogenic production on partitioning in the environment nor does it take into account biodegradation. The relevance of fugacity calculations for these substances is highly questionable.

### 3.2.5 New testing required

None

## 3.3 Ecotoxicity

### 3.3.1 Acute Toxicity to Fish

Only ECOSAR calculated values are available. The 96-hr LC50 for citronellol is calculated to be 10.7 mg/L while geraniol and nerol are calculated to be about an order of magnitude lower (0.57 mg/L) because these are treated by ECOSAR as vinyl alcohols even though they are not. They are 2,3-alkenols and ought to be treated, more appropriately, as neutral organics. If so, their acute toxicity should be very similar to citronellol. The LC50 for acetylated myrcene (principally geranyl acetate) can be estimated from its components. The calculated LC50 for geranyl acetate and neryl acetate is 1.4 mg/L while for limonene; the measured 96-hr LC50 in bluegill fish is 37 mg/L [Watkins *et al.*, 1985]. This latter value can be compared to the ECOSAR calculated value of 0.39 mg/L to demonstrate the conservative nature of the models. Because of the lack of data on this group, conducting an assay with geraniol should validate the QSAR algorithm for the three structurally related terpenoid primary alcohols. The results of this study can be compared to calculated 96-hr LC50 data for citronellol and calculated 96-hr LC50 data for geraniol and nerol as neutral organics. Because geranyl acetate and neryl acetate will be readily hydrolysed to nerol and geraniol, and the value for limonene is known, it is not necessary to conduct testing on acetylated myrcene.

### 3.3.2 Acute Toxicity to Aquatic Invertebrates

Only an ECOSAR calculated value is available for citronellol and at 12.4 mg/L (48-hr Daphnia), it does not differ significantly from that for fish. Because geraniol and nerol are treated by ECOSAR as vinyl alcohols even though they are not, there are insufficient data on structurally related substances to calculate the acute toxicity to invertebrates. They more appropriately ought to be treated as neutral organics. If so, their acute toxicity should be very similar to citronellol. The 48-hr Daphnia LC50 for acetylated myrcene can be estimated from its components. The calculated 48-hr LC50 for geranyl acetate or neryl acetate is 0.86 mg/L, while for limonene the measured 48-hr LC50 in Daphnia pulex is 37 mg/L [Passino and Smith, 1987]. As in the case of acute toxicity to fish, this latter

value can be compared to the ECOSAR calculated value of 0.50 mg/L to demonstrate the conservative nature of the models. Because of the lack of data on this group, the QSAR algorithm should be validated by conducting a test on geraniol (the same one as chosen above). It is not necessary to conduct testing on acetylated myrcene, because geranyl acetate and neryl acetate are expected to be readily hydrolysed to nerol and geraniol, and the value for limonene is known.

### 3.3.3 Acute Toxicity to Aquatic Plants

In addition to ECOSAR calculated EC50 values, experimental data the three terpenoid primary alcohols and citral are available. Citronellol, geraniol, nerol, and citral were subjected to a plate inhibition assay using concentrations of 100, 1000 or 10,000 mg/L [Ikawa *et al.*, 1992]. In this experiment, three disks containing the above solutions were applied to *Chlorella p*-seeded agar plates that were then placed under a fluorescent light for 48-hr. At 10,000 mg/L, each of the four substances showed a complete wipe out of the yellow-green lawn color of *Chlorella p*. At 1000 mg/L, citronellol showed no effect on growth while geraniol and nerol showed a lightening of lawn color compared to control plates. At 1000 mg/L, citral showed complete wipe out of lawn color. At 100 mg/l, geraniol, nerol, and citral show no inhibitory effect on growth. Inhibition appeared to take place through the vapor phase rather then by diffusion through the agar medium in that inhibition also occurred when the solution disks were separated from the agar surface by Teflon disks.

ECOSAR calculated 96-hr EC50 is available for citronellol and at 8.2 mg/L it does not differ significantly from the calculated values for fish or Daphnia. Because geraniol and nerol are treated by ECOSAR as vinyl alcohols even though they are not, there are insufficient data on structurally related substances to calculate the acute toxicity to algae. More appropriately, they ought to be treated as neutral organics. If so, their acute toxicity to algae should be very similar to citronellol. The algal EC50 for acetylated myrcene (geranyl acetate) can be estimated from its components. The calculated 96-hr EC50 for geranyl acetate and neryl acetate is 0.12 mg/L while for limonene it is 0.36 mg/L.

The experimental data for cited for citronellol, geraniol, nerol, and citral indicates a very low order of acute toxicity to algae. No inhibition to growth was observed at 100 mg/L for any of the four substances [Ikawa *et al.*, 1992]. These experimental NOE values are approximately two orders of magnitude greater than ECOSAR calculated EC50 values, demonstrating the conservative nature of the model. Based on these results it is not necessary to perform any further testing for this endpoint.

### 3.3.4 New Testing Required

- Acute toxicity to fish by OECD guideline 203 for geraniol.
- Acute toxicity to Daphnia by OECD guideline 202 for geraniol.

## 3.4 Human Health Data

### 3.4.1 Acute Toxicity

Rat oral LD50 values are available for citronellol, geraniol and nerol and are all in the same range. All indicate these materials to be very low in oral acute toxicity with values ranging from 3450 mg/kg to 6330 mg/kg [Moreno, 1972, 1973; Yamawaki, 1962; Jenner, 1964]. Rabbit dermal LD50 values are similarly very low. Values are in range from 2650 mg/kg to 5000 mg/kg [Moreno, 1972, 1973]. The mouse inhalation ED25 values are likewise low [Troy, 1977]. No data are available for acetylated myrcene; however, the LD50 values for the all of the major components are known and are all in the range of 5000 mg/kg.

### *3.4.2* Genotoxicity *in vitro* and *in vivo*

#### *3.4.2.1* *In vitro*

*In vitro* genotoxicity assays available for citronellol, geraniol, citral (geranial and neral mixture) and acetylated myrcene (geranyl acetate and neryl acetate mixture) demonstrate that these substances have a low genotoxic potential. In standard Ames assays, various strains of *Salmonella typhimurium* were incubated with concentrations of geraniol up to and including 5000 µg/plate [Eder *et al.*, 1980; Florin *et al.*, 1980; Ishidate *et al.*, 1984;

Heck *et al.*, 1989]. No mutagenic effects were reported in any study. No evidence of mutagenicity was reported in an Ames assay with citronellol metabolites [Rockwell and Raw, 1979]. In two chromosomal aberration assays with geraniol and a geranial/neral mixture, there was no evidence of increased incidence of chromosomal aberrations when Chinese hamster lung fibroblasts were incubated with 125 µg/plate of geraniol or 30 µg/plate of the geranial/neral mixture, respectively [Ishidate *et al.*, 1984]. Nerol, being a geometrical isomer of geraniol would also be expected to be negative. The acetates of nerol and geraniol, the principal constituents of acetylated myrcene, which will hydrolyse to nerol and geraniol, have also been tested and found to be negative in Ames assays at concentrations up to 20,000 µg/plate [Mortelmans *et al.*, 1986; Heck *et al.*, 1989]. Also, there was no evidence of unscheduled DNA synthesis when 100 nl/ml of geranyl acetate was incubated with freshly prepared rat hepatocytes [Heck *et al.*, 1989]. The only other major component of acetylated myrcene is limonene, which is also negative in *in vitro* genotoxicity assays.

*3.4.2.2 In vivo*

*In vivo* tests on citronellol and acetylated myrcene (geranyl acetate) confirm the lack of genotoxic potential. A mixture of geranyl acetate (79%) and citronellyl acetate (21%) showed no evidence of increased micronuclei in a standardized mouse (B6C3F1 strain) micronucleus assay at dose levels up to and including 1800 mg/kg bw [Shelby *et al.*, 1993] and there was no evidence of unscheduled DNA synthesis when the geranyl acetate/citronellyl acetate mixture was given orally to Fisher F344 rats [Mirsalis *et al.*, 1983]. Since these esters hydrolyze to geraniol and citronellol in rodents [Grundschober, 1977; Heymann, 1980], these results apply directly to geraniol and citronellol. In an attempt to assess the mutagenicity of urinary metabolites of citronellol, an Ames assay was performed on the urine of rats given oral doses of 100 ul of citronellol. No mutagenic effects were reported [Rockwell and Raw, 1979]. Results of studies for the mixture of geranyl and citronellyl acetate and citronellol confirm that these terpenoid alcohols and related ester exhibit low genotoxic potential *in vivo*.

### 3.4.3 Repeat Dose Toxicity

#### *3.4.3.1 Short-term studies*

Citronellol, as an equal mixture with the structurally similar material linalool, administered to rats at 100 mg/kg/day for 12 weeks, resulted in no adverse effects [Oser, 1958]. Geraniol, in combination with a structural isomer, was administered to groups of rats (5/sex/group) in the diet at concentrations of 10,000 ppm for 16 weeks or 1000 ppm for 27 weeks. No adverse effects were reported in either study [Hagan *et al.*, 1967]. No adverse effects were reported when Osborne-Mendel rats (10/sex/group) were maintained on diets resulting in an average daily intake of 200 mg/kg bw/day for 91 days [Hagan *et al.*, 1967]. For 17 weeks, Osborne-Mendel rats (10/sex/group) were maintained on diets containing 1000, 2,500, or 10,000 ppm of geranyl acetate (acetylated myrcene). The dietary concentrations were calculated to provide average daily intakes of 50, 125, or 500 mg/kg bw. No effects were reported in the study [Hagan *et al.*, 1967]. Likewise, no adverse effects were observed when rats were maintained on a diet calculated to provide an estimated average daily intake of greater than 200 mg/kg bw/day of citral, a mixture of geranial and neral, for 91 days [Hagan *et al.*, 1967].

#### *3.4.3.2 Long-term studies*

A mixture of geranyl acetate (79%) and citronellyl acetate (21%), which would be hydrolysed to geraniol and citronellol, respectively, has been the subject of 14 day, 13-week and 103-week oral (gavage) repeat dose studies in both rats and mice conducted by the National Toxicology Program [NTP, 1987]. According to the authors, "Under conditions of the 2-year bioassay there was no evidence of carcinogenicity when male and female Fisher F344 rats were administered 2000 mg/kg bw/day of a mixture of geranyl acetate and citronellyl acetate by gavage" [NTP, 1987]. Similarly, there was no evidence of carcinogenicity when both sexes of B6C3F1 mice were administered 1000 mg/kg bw/day by gavage for 103 weeks.

### 3.4.4 Reproductive Toxicity

Data on reproductive toxicity is available for a mixture of geranial and neral, *trans*- and *cis*-3,7-dimethyl-2,6-octadienal, respectively. Geraniol and nerol are rapidly oxidized to form geranial and neral, respectively, *in vivo*. Given that the mixture of aldehydes exhibits a higher level of toxicity than the corresponding alcohols geraniol and nerol (see Robust Summaries for Repeat Dose and Acute Toxicity), data on reproductive and developmental toxicity for the aldehydes may be used to conservatively estimate reproductive toxicity for the corresponding alcohols.

A mixture of geranial and neral has been subjected to an oral 2-generation reproductive study in rats. There were no reproductive effects at the maternal NOAEL of 50 mg/kg/day and a fetal/pup NOAEL of 160 mg/kg bw/day. At a maternally toxic level of 500 mg/kg bw/day, the only effect reported was a slightly decreased pup weight [Hoberman *et al.*, 1989].

In a developmental/reproduction screening study, four groups of 10 virgin Crl CD female Sprague-Dawley rats were administered the acetal formed from citral (geranial and neral mixture) and ethanol. The acetal will readily hydrolyze to citral. Dose levels of 0, 125, 250, or 500 mg/kg bw/day test material was given by gavage once daily, 7 days prior to cohabitation, through cohabitation (maximum of 7 days), gestation, delivery, and a 4-day post-parturition period. The duration of the study was 39 days. Maternal indices monitored included twice-daily observation, measurement of body weights, food consumption, duration of gestation, and fertility parameters (mating and fertility index, gestation index, number of offspring per litter). Offspring indices included daily observation, clinical signs, examination for gross external malformations, and measurement of body weight. Based on these measurements the NOAELs for maternal toxicity and developmental toxicity were reported to be 125 and 250 mg/kg bw/day, respectively [Vollmuth *et al.*, 1995].

### 3.4.5 Developmental/Teratogenicity Toxicity

A geranial/neral mixture has been subjected to an oral feto-toxicity study and an inhalation developmental study in rats. In the feto-toxicity study, female Wistar rats were administered dose levels of 0, 60, 125, 500, and 1000 mg/kg bw of a geranial/neral mixture in corn oil daily by gavage during days 6-15 of pregnancy. A NOAEL for maternal and developmental toxicities were reported to be 60 mg/kg bw/day [Christina *et al.*, 1995]. In the inhalation developmental study, groups of female Sprague-Dawley rats were exposed to atmospheres containing up to 85 ppm of a geranial/neral mixture 6 hours daily during days 6-15 of gestation. A NOAEL for maternal toxicity was reported to be 35 ppm. There were some slight fetotoxic effects at the maternally toxic level of 85 ppm (as a vapor/aerosol) [Gaworski *et al*., 1992]. The materials in this group would not be expected to differ significantly in developmental or reproductive toxicity studies.

### 3.4.6 New Testing Required

None

## 3.5 Test Plan Table

| Chemical | Physical-Chemical Properties | | | | |
|---|---|---|---|---|---|
| | **Melting Point** | **Boiling Point** | **Vapor Pressure** | **Partition Coefficient** | **Water Solubility** |
| **CAS No. 106-22-9** 3,7-Dimethyl-6-octen-1-ol (dl-Citronellol) | NA | A | A | A | A, Calc |
| **CAS No. 106-24-1** *trans*-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol) | NA | A | Calc | Calc | A, Calc |
| **CAS No. 106-25-2** *cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol) | NA | A | Calc | Calc | Calc, R |
| **CAS No. 68412-04-4** 3,7-Dimethyl-2,6-octadien-1-yl acetate (Acetylated myrcene) | NA | A | Calc, R | Calc, R | Calc, R |

| Chemical | Environmental Fate and Pathways | | | |
|---|---|---|---|---|
| | **Photodegradation** | **Stability in Water** | **Biodegradation** | **Fugacity** |
| **CAS No. 106-22-9** 3,7-Dimethyl-6-octen-1-ol (dl-Citronellol) | Calc | NA | A | Calc |
| **CAS No. 106-24-1** *trans*-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol) | Calc | NA | A | Calc |
| **CAS No. 106-25-2** *cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol) | Calc | NA | R | Calc |
| **CAS No. 68412-04-4** 3,7-Dimethyl-2,6-octadien-1-yl acetate (Acetylated myrcene) | R | A, Calc | A | Calc |

| Chemical | Ecotoxicity | | |
|---|---|---|---|
| | **Acute Toxicity to Fish** | **Acute Toxicity to Aquatic Invertebrates** | **Acute Toxicity to Aquatic Plants** |
| **CAS No. 106-22-9**<br>3,7-Dimethyl-6-octen-1-ol (dl-Citronellol) | R, Calc | Calc, R | A, Calc, R |
| **CAS No. 106-24-1**<br>*trans*-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol) | Test, Calc | Test | A, Test |
| **CAS No. 106-25-2**<br>*cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol) | Calc, R | R | A, R |
| **CAS No. 68412-04-4**<br>3,7-Dimethyl-2,6-octadien-1-yl acetate (Acetylated myrcene) | R | R | R |

| Chemical | Human Health Data | | | | | |
|---|---|---|---|---|---|---|
| | **Acute Toxicity** | **Genetic Toxicity *In Vitro*** | **Genetic Toxicity *In Vivo*** | **Repeat Dose Toxicity** | **Repro-ductive Toxicity** | **Develop-mental Toxicity** |
| **CAS No. 106-22-9**<br>3,7-Dimethyl-6-octen-1-ol (dl-Citronellol) | A | A | R | A | R | R |
| **CAS No. 106-24-1**<br>*trans*-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol) | A | A | R | A | R | R |
| **CAS No. 106-25-2**<br>*cis*-3,7-Dimethyl-2,6-octadien-1-ol (Nerol) | A | R | R | R | R | R |
| **CAS No. 68412-04-4**<br>3,7-Dimethyl-2,6-octadien-1-yl acetate (Acetylated myrcene) | A | A | A | A | R | R |

## Legend

| Symbol | Description |
|---|---|
| R | Endpoint requirement fulfilled using category approach, SAR |
| Test | Endpoint requirements to be fulfilled with testing |
| Calc | Endpoint requirement fulfilled based on calculated data |
| A | Endpoint requirement fulfilled with adequate existing data |
| NR | Not required per the OECD SIDS guidance |
| NA | Not applicable due to physical/chemical properties |
| O | Other |

# 4 References for Test Plan and Robust Summaries


Abas R. and Hayton, W. L. (1997) A physiologically based pharmacokinetic and pharmacodynamic model for paraoxon in rainbow trout. *Toxicol. Appl. Pharmacol.,* **145**, 192-201.

Anders M. W. (1989) Biotransformation and bioactivation of xenobiotics by the kidney. *Intermediary Xenobiotic Metabolism in Animals.* Edited by D. H. Hutson, J. Caldwell, and G. D. Paulson. p. 81-97. Taylor and Francis, New York.

Asano M. and Yamakawa, T. (1950) The fate of branched chain fatty acids in the body. I. A contribution to the problem of "Hildebrandt Acid". *Journal of Biochemistry*, Tokyo, **37**, 321-327.

Barron M. G., Charron K. A., Stott W. T., Duvall S. E. (1999) Tissue carboxylesterase activity of rainbow trout. *Environmental Toxicology and Chemistry*, **18,** 2506-2511.

Bauer K. and Garbe D (1985) *Common Flavor and Fragrance Materials* Verlagsgesellschaft mbH, D-6940, Weinheim, Federal Republic of Germany.

Birch R. R. and Fletcher, R. J. (1991) The application of dissolved inorganic carbon measurements to the study of aerobic biodegradability.*Chemosphere,* **23(4),** 507-524.

Boone J. S. and Chambers, J. E. (1996) Time course of inhibition of cholinesterase and aliesterase activities and nonprotein sulfhydryl levels following exposure to organophosphorous insecticides in mosquito fish (Gambusia affinis). *Fundam. Appl. Toxicol*. **29**, 203-207.

Boyer S. C. and Petersen, D. R. (1990) The metabolsism of 3,7-Dimethyl-2,6-Octadienal (citral) in rat hepatic mitochondrial and cytosolic fractions: Interactions with aldehyde and alcohol dehydrogenases. *Drug Metabolism and Disposition,* **18**, 81-86.

Bush Boake Allen, Inc (BBA) (1990) Biodegradability of geraniol and d,l-citronellol. Private communication to FMA.

Chadha A. and Madyastha, K. M. (1984) Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. *Xenobiotica,* **14**, 365-374.

Chadha A. and Madyastha, K. M. (1982) Omega-hydroxylation of acyclic monoterpene alcohols by rat lung microsomes. *Biochemical and Biophysics Research Communications,* **108**, 1271-1277.

Cristina A., Nogueira, A.M., Carvalho, R., Souza, A., Chahoud, I., Paumgartten, F. (1995) Study on the embryofeto-toxicity of citral in the rat. *Toxicology*, **96**, 105-113.

Curtis R. O. (1982) A simple density index for Douglas-fir. *Forest Science,* **28,** 92-94.

Curtis R. O. (1994) Some simulation estimates of mean annual increment of Douglas-fir: Results, limitation, and implications for management. Research Paper PNW-RP-471. Portland OR: Pacific Northwest Research Station. Forest Service, USDA. p. 27.

Diliberto J. J., Srinivas, P., Overstreet, D., Usha, G., Burka, L. T., and Birnbaum, L. S. (1990) Metabolism of citral, an a,b-unsaturated aldehyde, in male F344 rats. *Drug Metabolism and Disposition,* **18**, 866-875.

Diliberto J. J., Usha, G. and Birnbaum, L. S. (1988) Disposition of citral in male Fischer rats. *Drug Metabolism and Disposition,* **16**, 721-727.

Eder E., Nedecker, T., Lutz, D., Henschler, D. (1980) Mutagenic potential of allyl and allylic compounds. *Biochemical Pharmacology,* **29**, 993-998.

Fischer F.G. and Bielig, H.J. (1940) On the hydrogenation of unsaturated substances in the animal body. *Physiol. Chem.*, **266(1/3),** 73-98.

Florin I., Rutberg, L., Curvall, M., and Enzell, C.R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames test. *Toxicology,* **18**, 219-232.

Fragrance Materials Association (FMA). Reported values for boiling point.

Fragrance Materials Association (FMA). Reported values for vapor pressure.

Gaworski C.L., Vollmuth, T.A., York, R.G., Heck, J.D., Arany, C. (1992) Developmental toxicity evaluation of inhaled citral in rats. *Food Chemical Toxicology*, **30** 269-275.

Givaudan-Roure (1989) Determination of the ready biodegradability of d,l-citronellol. Unpublished report to FMA.

Givaudan-Roure (1991) Partition coefficient n-octanol/water of d,l-citronellol. Private communication to FMA.

Grundschober F. (1977) Toxicological assessment of flavoring esters. *Toxicology,* **8**, 387-390.

Guenther E. (1952) Essential Oil of the Plant Family Pinaceae in “the Essential Oils” edited by E. Guenther **IV**, pp. 201-307. Van Nostrand Reinhold Co., New York.

Hagan E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.A., and Brouwer, J.B. (1967) Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food Cosmetic Toxicology,* **5**, 141-157.

Hall R.L. and Oser, B.L. (1965) Recent progress in the consideration of flavoring ingredients under the food additives amendment. III GRAS Substances. *Food Technology,* **19**, 151-197.

Haseman J.K., Winbush, J.S. and O'Donnell, M.W., Jr. (1986) Use of dual control groups to estimate false positive rates in laboratory animal carcinogenicity studies. *Fundam. and Appl. Toxicol.,* **7**, 573-584.

Heck J. D., Vollmuth, T. A., Cifone, M. A., Jagannath, D. R., Myhr B., and R.D. Curren (1989). An evaluation of food flavoring ingredients in a genetic toxicity screening battery. *The Toxicologist***, 9(1**), 257.

Heil T. P. and Lindsay, R. C (1990) Environmental and industrial factors relating to flavor tainting of fish in the upper Wisconsin river. *Journal of Environmental Science and Health*, **B25(4),** 527-552.

Heymann E. (1980) Carboxylesterases and amidases. In Enzymatic Basis of Detoxication. Edited by W.B. Jakoby. 2nd Ed. 291-323. Academic Press, New York.

Hoberman A.M., Christian, M.S., Bennett, M.B. and Vollmuth, T.A. (1989). Abstract. Oral general reproduction study of citral in female rats. *The Toxicologist,* **9**, 271.

Ikawa M., Mosley S., and Barbero, L. (1992) Inhibitory effects of terpene alcohols and aldehydes on growth of green alga Chlorella pyrenoidosa. *Journal of Chemical Ecology,* **18**(10),1755-1760.

Ishida T., Toyota, M. and Asakawa, Y. (1989) Terpenoid biotransformation in mammals. V. Metabolism of (+)-citronellal, 7-hydroxycitronellal, citral, (-)-perillaldehyde, (-)-myrtenal, cuminaldehyde, thujone, and carvone in rabbits. *Xenobiotica,* **19**, 843-855.

Ishidate M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A. (1984) Primary Mutagenicity Screening of Food Additives Currently Used in Japan. *Fd. Chem. Toxic.,* **22**, 623-636.

Jenner P.M., Hagan, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. (1964) Food flavorings and compounds of related structure I. Acute Oral Toxicity. *Fd Cosmet. Toxicol*. **2**, 327-343.

Johnson S. and Cain, J. (1937) Terpene concentrations in Western Douglas fir. *Journal of American Pharmaceutical Association*, **26**, 406.

Klimisch H. J., Andreae, M., and Tillman, U. (1997) A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Journal of Regulatory Toxicology and Pharmacology*, **25**, 1-5

Larson B., Bonboi-Mingarro, T., Brancaleoni, E., Calogirou, A., Cecinato, A., Coeur, C., Chatzianestis, I., Dusne, M. Frattoni, M., Fugit, J., hanson, U., Jacob, V., Mimkos, N., Hoffman, T.m, Owen, S.,m Perez, R., Reichmann, A., Seufert, G., Staudt, M., Steinbrecher, R. (1997) Sampling and analysis of terpenes in Air. An interlaboratory comparison. *Atomospheric Environment*, **31(1),** 35-49.

Leinweber F. J. (1987) Possible physiological roles of carboxylic ester hydrolases, *Drug Metabolism Review*, **18**, 379-439.

Lewis D.F., Ioannides, C., Walker, R., and Parke, D. V. (1994) Safety evaluations of food chemicals by "compact" 1. A study of some acyclic terpenes, *Fd. Chem. Toxic.,* **32**, 1053-1059.

Licht H. and Corsia, C. J. (1978) Cytochrome P-450LM2 mediated hydroxylation of monoterpene alcohols. *Biochemistry,* **17**, 5638-5646.

Mackay D. (1991) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Merck & Co., Inc. The Merck Index (1997) Published by Merck Research Laboratories, 12$^{th}$ edition, Whitehouse Station, NJ.

Mirsalis J., Tyson, K., Beck, J., Loh, E., Steinmetz, K., Contreras, C., Austere, L.,Martin, S., and Spalding J. (1983). Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. *Environmental Mutagenesis,* **5(3)**, 482.

Moreno O. M. (1972) Acute oral toxicity of nerol in rats and rabbits. Unpublished report to RIFM.

Moreno O. M. (1973) Acute oral toxicity studies on rats and rabbits. Unpublished report to RIFM.

Mortelmans K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., and Zeiger, E. (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environmental Mutagenesis* **8(7),** 1-119.

National Toxicology Program (NTP) (1987) Carcinogenesis studies of food grade geranyl acetate (71%) and citronellyl acetate (29%). NTP-TR-252. National Technical Information Services. PB-88-2508.

Oser B. L. (1958) Toxicological Screening of Components of Food Flavors Class VI. Citronellol and Linalool. Food and Drug Research Laboratories. Private communication to FEMA.

Parke D. V. and Rahman, H. (1969) The effects of some terpenoids and other dietary nutrients on hepatic drug-metabolizing enzymes. *Biochemical Journal,* **113**, 12.

Passino D. R. and Smith, S. (1987) Acute bioassays and hazard evaluation of representative contaminants detected in great lakes fish. *Environmental Toxicology and Chemistry*, **6(1),** 90-1907.

Phillips J. C. Kingsnorth, J., Gangolli, S. D. and Gaunt, I. F. (1976) Studies on the absorption, distribution and excretion of citral in the rat and the mouse. *Fd. Chem. Toxic.,* **14**, 537-540.

Quest International Ltd. (1994) The ultimate biodegradability of citronellol in the sealed vessel test. Private communication to FMA.

Rockwell P. and Raw, I. (1979) A mutagenic screening of various herbs, spices, and food additives. *Nutrition and Cancer*, **1**, 10-15.

Shelby M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol; results with 49 chemicals. *Environmental and Molecular Mutagenesis*, **21,** 160-179.

Stein E. (1986) Lipids, lipoproteins, and apolipoproteins. in "Textbook of Clinical Chemistry" edited by N. Tietz. p. 829-895. W.B. Saunders Company, Philadelphia, PA.

Stofberg J. and Grundschober, F. (1987) Consumption ratio and food predominance of flavoring materials. *Perfumer and Flavorist,* **12**, 27.

Stofberg J. and Kirschman, J.C. (1985) The consumption ratio of flavoring materials: A mechanism for setting priorities for safety evaluation. *Fd. Chem. Toxic.,* **23**, 857-860.

Syracuse Research Corporation (SRC) Private communication to FMA.

Troy W.R. (1977) Doctoral Dissertation: The comparative respiratory irritation potential of fourteen fragrance raw materials. Unpublished report to RIFM.

TSCA - Toxic Substances Control Act (1990) IUR Report of Annual Industrial Production.

Voet D. and Voet, J. G. (1990) Biochemistry. John Wiley & Sons, NY.

Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology 41(5): 597.

Vuilleumier C., Flament, I., Sauvegrain, P. (1995) Headspace analysis study of evaporation rate of perfume ingredients applied onto skin. *International Journal of Cosmetic Science,* **17**, 61-76.

Watkins C., Thayer, D., and Haller, W. (1985) Toxicity of adjuvants to bluegill. *Bulletin of Environmental Contamination and Toxicology,* **34(1),** 138-142.

Wiess R. (1959) International Flavors and Fragrances, Inc. US Patent 2882323.

Williams R. T. (1959) Detoxication Mechanisms. Second Edition. p. 88-113. Edited by Chapman and Hall Ltd. London, England.

Yamawaki T. (1962). Pharmacological effects of geraniol. Nippon *Yakurigaku Zasshi*, **58**, 394-400.

Yoshiaki O., Ninagawa, Y. Fujita, Y., Hosogai, T., Nishida, T., Tamai, Y., and Itoi, K (1973) Kuraray Co., Ltd. JA 758004. *Chemical Abstracts,* **83**, 97637n (1975).